## REMARKS/ARGUMENTS

Amendments which add two paragraphs to the specification are presented as Amendment A and Amendment B above.

Claims 5, 7-21, 29-34, and 35-40 are presented for examination. Claims 5, 7-21, 29-34 are pending. Claims 35-40 are newly presented. Claims 5 and 29 would be amended. In view of the restriction requirement and election, claims 14 to 21 are canceled without prejudice.

Claims 5, 7, and 7-13 stand rejected on the grounds of an alleged lack of enablement with respect to the recital of "preventing."

Claim 29 stands rejected on the grounds of an alleged lack of enablement with respect to the breadth of the compounds encompassed.

Claims 5 and 29 stand rejected allegedly under the judicially created doctrine of double-patenting over claim 30 of co-pending application 09/944.049.

Claims 29-33 stand rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Protiva et al. (4,243,805) in view of the Merck Manual of Diagnosis (17th Ed.).

Claims 29-34 stand rejected under 35 U.S.C. §103(a) as being allegedly unpatentable over Sindelar et al. in view of the Merck Manual of Diagnosis (17th Ed.) .and Michelson.

Applicants respond to the above rejections below.

The Restriction Requirement

Applicants thank the Examiner for reconsidering the restriction requirement and rejoining Groups I and III.

Support for Amendment A and Amendment B to the Specification

The *Cross-References to Related Applications* section of the instant specification incorporates by reference U.S. Patent Application No. 09/944,049. The '049 application

(enclosed with the present IDS) is already of record. This application corresponds to the U.S. patent application filed on August 30, 2001 titled "Inhibition of CMV infection and Dissemination (Attorney Docket No. 019934-002510US/PCT).

The '049 application recites therein at p. 38 the paragraph to be added as Amendment A.

The '049 application recites therein at the bottom of p. 33 the paragraph to be added as Amendment B.

In view of the above, Applicants submit that the amendment adds no new matter and respectfully request its entry.

Support for Amendments to the Claims.

Claim 5 would be further amended to recite "A method for inhibiting dissemination of CMV in a human, comprising administering to the human an effective amount of a small organic compound having a molecular weight of less than 800 daltons and which blocks or inhibits the binding of a chemokine to a US28 receptor or a US28 receptor fragment and wherein said administering slows the progression of CMV viral dissemination in the human." Support for the "human" subject matter is found in the original version of the claim. Support for the " small organic compound having a molecular weight of less than 800 daltons" subject matter is found in the newly added paragraph to the specification at lines 3 and 4. Support for the "receptor" subject matter is found *inter alia* at p. 8, line 23. Support for the recital of "inhibiting dissemination" subject matter is found in the specification *inter alia* at p. 8, lines 15-16, and p.8, last paragraph, and at p. 13 at paragraphs 3 and 4. Support for the slowing progression subject matter is specifically found in the specification *inter alia* at p. 13, line 18.

Claim 29 would be amended to recite:

> A method for treating CMV infection in a human, comprising administering to the human an effective amount of a US 28 receptor modulator capable of blocking or inhibiting the binding of a chemokine to the US28 receptor, wherein said modulator is a small organic compound having a molecular weight

of less than 800 daltons and said administering slows the progression of CMV dissemination in the human.

Support for this subject matter is found in the specification *inter alia* at p. 16, first through last full paragraph. Support for the subject matter of a US28 receptor modulator is found *inter alia* in the Title and Abstract of the specification. Support for the subject matter of " wherein said administering slows the progression of CMV dissemination in the human" is found in the specification at p. 13 at paragraphs 3 and 4. Support for the subject matter of a "small organic compound having a molecular weight of less than 800 daltons" is found in the newly added paragraph to the specification at lines 3 and 4. Support for the "capable of" recital is found in the previous version of the claim.

New claims 35 and 36 depend from claims 29 and 5 respectively and would recite "wherein the molecular weight is between 300 and 600 daltons." Support for this subject matter is found in the newly added paragraph to the specification at lines 3 and 4.

New claim 37 depends from claim 29 and would recite "wherein said method the progression of viral dissemination via a CMV-infected leukocyte is slowed." Support for the leukocyte subject matter is found *inter alia* in the specification at p. 8, line 12.

New claim 38 depends from claim 5 and would recite "wherein said method the progression of viral dissemination via a CMV-infected leukocyte is inhibited." Support for the leukocyte subject matter is found *inter alia* in the specification at p. 8, line 12.

New claims 39 and 40 depend respectively from base claims 29 and 5 and would be amended to recite "wherein the chemokine is fractalkine." Support for this subject matter is found in the specification at p. 13, fourth full paragraph.

In view of the above, Applicants believe the amendments add no new matter and respectfully request their entry.

Response to the Rejection of Claims 5, and 7-12 for an Alleged Lack of Enablement

The Examiner considered "preventing dissemination" as only meaning "preventing dissemination of CMV in a human totally, absolutely, or permanently" and as such to be "highly unlikely." Without acquiescing to the position of the Examiner but for sake of

expediting prosecution of the application, Applicants have amended the base claim to recite "inhibiting" in place of "preventing." The body of the claim has also been amended to recite the term "inhibiting." Applicants submit that the term "inhibiting" would not be limited "to preventing dissemination of CMV in a human totally, absolutely, or permanently."

In view of the above, Applicants request that the above rejection be reconsidered and withdrawn.

Response to the Rejection of Claim 29 for Alleged Lack of Enablement

Claim 29 stands rejected as allegedly not enabled as to the breadth of the encompassed compounds. Applicants respond to the *Wands* analysis below.

*Nature of the Invention*

The subject matter of claim 29 is in the therapeutic arts and concerns methods of treating CMV infection in a human by administering US28 receptor modulators capable of blocking or inhibiting the binding of a chemokine to a US28 receptor.

The invention is drawn to novel *methods of treatment,* not the compounds themselves. As recited at p. 8 line 26 of the specification, "the present invention provides a novel mechanism for control of cytomegalovirus induced disease." A point of novelty is in the method of treatment according to that mechanism (e.g., inhibiting the binding of chemokines to the US28 receptor thereby inhibiting or slowing the migration or dissemination of the virus).

*Enablement Standard for NON-inventive Subject Matter*

The enablement requirement of §112 demands that U.S. patent applicants teach how to make and use their invention with sufficient detail that one of skill can practice the invention without undue experimentation. The key to applying this law when examining method claims is to focus on the inventive features of the claims and not on ancillary aspects.

Ancillary aspects of patent claims to methods can properly include applying the method in circumstances where the user must first identify novel and unique elements such as a

variety of therapeutic compounds, including but not limited to the modulators recited in claim 29. But so long as the claimed method is novel, non-obvious and adequately taught, it is patentable. The fact that the claimed method might be used on undisclosed modulators is irrelevant to the enablement requirement.

There are legal precedents for this focused approach to applying the enablement requirement. With regard to the amount of enablement required for inventive features of a claim versus the amount of teaching needed to describe non-inventive features of a claim, there are at least three important court decisions which expressly relax the enablement requirement for non-inventive aspects of patent claims. Of the three cases, *In re Lange*, 209 USPQ 288 ( CCPA, 1981), is the most recent.

In *Lange*, the invention related to the use of electronegative gases to coat electrical devices to dampen arcing (sparks). The Examiner noted that the claims were broad enough to read on casting of electrodes and that the disclosure was limited to coating of preexisting electrodes. Convinced that this single species was not easily obtainable, the Examiner refused to allow the claims due to over breadth.

In rejecting the position of the Patent Office, the CCPA noted that the invention is the use of the gases to dampen sparks. No claim was drawn to casted electrodes. The entire claims were allowed and the CCPA stated:

> However, although appellant can be required to limit his claims to that subject area which is adequately disclosed, the existence of species which are not adequately disclosed does not require that the entire application be found nonenabling. See In re Cook, 58 CCPA 1049, 439, F.2d 730, 169 USPQ 298 (1971). This is especially true in this case where, as stated by appellant at oral argument, the method of forming the electrodes is **not the inventive principle** [Emphasis added].

The other two cases are *In Application of Fuetterer*, 138 USPQ 217 (CCPA 1963) and *Application of Herschler*, 200 USPQ 711 (CCPA 1979). In *Herschler*, the applicant had discovered that dimethylsulfoxide (DMSO) was useful as a transdermal carrier for physiologically active steroids. The CCPA found that a priority application describing a single steroid (dexamethasone 21-phosphate) supported a claim to the genus of all steroids. Citing *Fuetterer*, the court explained that Herschler's claims were not drawn to a novel steroid but to the method of administration of steroids. As long as the class of steroids could be expected to be

carried across the skin by DMSO, the claim could encompass any steroid, known or unknown. As in *Fuetterer*, the CCPA reminded the Patent Office that the inventive principle was a method of administration of steroids and that the specific steroid exemplified was not the point of patentability.

*Herschler is* particularly on point with the facts of the present case. Like *Herschler*, the Applicants claim therapeutic methods involving the use of a variety of potential therapeutic agents. However, the therapeutic agents are not the invention. In *Herschler*, the invention was a method of passing steroids through the skin, and the claims were appropriately not limited to known steroids. Similarly, this invention lies in therapeutic methods of treating a patient by modulating the binding of chemokines to the US28 receptor or US fragments in order to inhibit or slow viral dissemination. The claims are methods claims drawn to methods of using compounds *not* the compounds themselves; and, thus, are not appropriately limited to just the exemplified compounds.

In contrast to the above cases, the *University of California v. Eli Lilly and Co.* 43 USPQ2d 1398 (Fed. Cir. 1997) case cited in the Action concerns *composition of matter* claims (e.g., a recombinant plasmid, a recombinant procaryotic microorganism) in which the point of novelty of the *composition* was the structure of the composition. Here, the major point of novelty lies in the *method* of treating CMV infection by achieving a certain function, i.e., blocking or inhibiting the binding of chemokines to the US28 receptor. The particular compounds used to achieve the function are ancillary to the invention. The *function* is the major point of novelty.

All of the above is to say nothing more than that the scope of the claims must *reasonably* match the scope of enablement.

*The Relative Skill of those in the Art*

The relative skill in the art is high as noted by the Examiner.

*Breadth of the Claims*

Without acquiescing to the position of the Examiner, Applicants have amended base claim 29. Claim 29 as amended recites:

> A method for treating CMV infection in a human, comprising administering to the human an effective amount of a US 28 receptor modulator capable of blocking or inhibiting the binding of a chemokine to the US28 receptor, wherein said modulator is a small organic compound of less than 800 daltons and said administering slows the progression of CMV dissemination in the human.

Applicants would amend claim 29 to recite a "modulator capable of blocking or inhibiting the binding of a chemokine to a US28 receptor" and to also recite " said administering slows the progression of CMV dissemination in the human." Thus, the base claim now expressly sets forth with particularity those elements which lie at a point of novelty as required by U.S.C. §112.

In addition, Applicants note that the base claim is now drawn in part to modulator subject matter of a "small organic compound having a molecular weight of less than 800 daltons."

*Amount of Guidance Provided*

A principal point of contention is that the claims recite a *functional* and not a *structural* limitation at the point of novelty. However, here it is the *functional* limitation which is at the major point of novelty.

With respect to the function, Applicants teach all the procedures necessary for one of ordinary skill in the art to practice the invention. It is not disputed that the specification teaches methods of screening compounds for the desired function and it teaches how such compounds can be administered to treat a CMV infection. With respect to methods for screening dissemination *in vivo,* the application incorporates by reference U.S. Patent Application No. 09/944,049 which teaches methods for screening dissemination *in vivo* using a primate model (see, for instance, the section therein starting at p. 43 and Example 5).

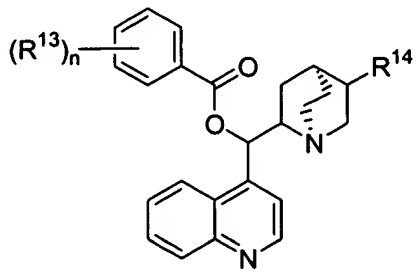
Moreover, even if one were to posit for the sake of argument that the genus of a "US 28 receptor modulator capable of blocking or inhibiting the binding of a chemokine to the

US28 receptor, wherein said modulator is a small organic compound of less than 800 daltons" must be enabled under a stricter standard, Applicants submit that such subject matter is enabled. The specification sets forth a number of patent applications which are incorporated by reference and which teach a great variety of structures and compounds of the recited size which are suitable for use as US28 receptor modulators.

For instance, U.S. Patent Application No. 09/944,049 (incorporated by reference in the first paragraph of the specification, and enclosed with the IDS submitted herewith) discloses broad classes of US28 modulators. For instance, at p. 38, this reference teaches:

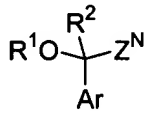
> In addition to antibodies, a variety of compounds can be used to inhibit US 28 or US28 homolog receptor-ligand interactions, including, without limitation, polypeptides, oligopeptides, polysaccharides, polynucleotides, lipids, small organic molecules (e.g., MW < 800, more preferably 300-600), and the like. Small organic molecules can be of a variety of chemical types including, but not limited to, sterols, nucleic acids, derivatives of purine and pyrimidine bases, β-lactams, aromatic compounds, heterocyclic compounds, carbocyclic compounds, oligo-N-substituted glycines, polycarbamates, oligosaccharides, lipids and amino acids, and derivatives and combinations thereof. Such compounds can be a natural product, a synthetic compound, or a chemical compound, or a combination of two or more substances. Typically, compounds are identified by high-through put screening of large libraries of compounds (e.g., combinatorial libraries). Methods for creating and screening such libraries are established and are described, for example, by Dolle and Nelson, J. (1999) *Combinatorial Chemistry* 1:235-282; Needels, *et al. Proc. Natl. Acad. Sci. USA, 90*: 10700 (1993); Ni, *et al J. Med. Chem., 39*: 1601 (1996); and in PCT publications WO 95/12608, WO 93/06121, WO 94/08051, WO 95/35503 and WO 95/30642, each of the foregoing references being incorporated herein by reference in its entirety for all purposes.

This application also sets forth preferred compounds of the formula:



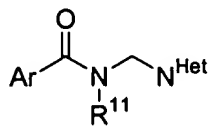
wherein the subscript n is an integer of from 0 to 3; each $R^{13}$ is independently selected from the group consisting of halogen, $NO_2$, CN, R, OR, $NR_2$, $CO_2R$, C(O)R, OC(O)R, NRC(O)R and $NRC(O)NR_2$, wherein each R is independently selected from H and $(C_1\text{-}C_8)$alkyl; and $R^{14}$ is selected from the group consisting of H and substituted or unsubstituted $(C_1\text{-}C_8)$alkyl. More preferably, $R^{14}$ is unsaturated $(C_2\text{-}C_8)$alkyl (e.g., alkenyl). Most preferably, $R^{14}$ is vinyl.

In addition, the present application claims priority benefit of U.S. Application No. 60/316,386 which is also incorporated by reference. This priority application is a priority application also for U.S. Patent Application No. 10/233,326 which was also incorporated by reference in the instant specification and is already of record. These applications disclose well over a hundred compounds of the formula




wherein Ar is a substituted or unsubstituted 5-14 membered heteroaryl group having from 1 to 5 heteroatoms as ring members; $R^1$ is selected from the group consisting of substituted or unsubstituted aryl$(C_1\text{-}C_4)$alkyl, heteroaryl$(C_1\text{-}C_4)$alkyl, $-C(O)R^{11}$, and $-C(O)NR^{11}R^{12}$, wherein each $R^{11}$ and $R^{12}$ independently is substituted or unsubstituted aryl, substituted or unsubstituted aryl$(C_1\text{-}C_4)$alkyl, substituted or unsubstituted $(C_4\text{-}C_8)$cycloalkyl$(C_1\text{-}C_4)$alkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroaryl$(C_1\text{-}C_4)$alkyl and substituted or unsubstituted hetero$(C_4\text{-}C_8)$cycloalkyl$(C_1\text{-}C_4)$alkyl; $R^2$ is H or $(C_1\text{-}C_8)$alkyl; and $Z^N$ is a substituted or unsubstituted hetero$(C_6\text{-}C_{10})$bicycloalkyl group.

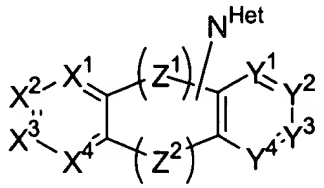
In addition, the instant specification incorporates by reference U.S. Patent Application No. 09/944,051 (see first paragraph of specification). This reference is already of record and discloses compounds of the general formula:



or a pharmaceutically acceptable salt thereof; wherein Ar represents a substituted aryl group; $R^{11}$ represents H or $(C_1\text{-}C_4)$alkyl; and $N^{Het}$ is a substituted or unsubstituted 4-, 5-, 6-, or 7-membered nitrogen heterocycle.

With respect to modulators of US28, the specification discloses (last paragraph at p. 12) other suitable compounds for use in the present invention (compositions and methods) as described in U.S. Patent No. 3,379,729 "Piperazinyldibenzothiepins" April 23, 1968 (already made of record) and U.S. Patent No. 4,444,778 (enclosed with the IDS submitted herewith). Still other related and useful dihydrodibenzo(b,f)thiepins are described in Jilek, et al., *Collect. Czech. Chem. Commun.* 33(6):1831-1845 (1968) (enclosed with the IDS submitted herewith). Each of the above references was incorporated by reference in the instant specification.

In addition, the present specification teaches compounds of the formula:




Thus, the specification discloses a large and varied collection of US28 receptor modulators in support of the recited modulator genus.

The Predictability of the Art

The Action also relies upon toxicity as a factor in assessing the predictability of the art. With respect to the toxicity of potential modulators, this concern has more do to with safety than whether an invention is operable. The courts have often emphasized that FDA regulatory criteria are **not** the criteria for patentability. An Applicant need not demonstrate clinical efficacy or safety. *See In re Brana*, 51 F.3d 1560 (Fed. Cir. 1995).

With respect to the ability of one of ordinary skill in the art to "fully recognize members of the genus," amended claim 29 recites methods of using US 28 receptor modulator to treat CMV infection. One of ordinary skill in the art would readily recognize whether or not a

use of a particular compound fell within the scope of claim 29. Means for screening such compounds for such modulatory activity are set forth in the specification and well known to one of ordinary skill in the art.

While Applicants are not presently claiming particular modulatory compounds themselves, the specification discloses well-populated diverse sets of such modulators. These incorporated references well exemplify for one of ordinary skill in the art small organic compound modulators suitable for use according to the invention.

Presence of Working Examples

The Action cites octoclothepin and methiothepin as the two sole working examples. Applicants submit that the above-discussed applications which were incorporated by reference disclose a great many additional working examples of compounds found to be US28 modulators.

In any case, limiting the scope of the invention to just the disclosed working examples and preferred embodiments is neither supported nor warranted either by case law precedent[1] or by the policies underlying the patent laws. For example, in *In re Goffe*, 191 U.S.P.Q. 429, 431 (C.C.P.A. 1976), method claims involving the use of an "agglomerable" material were rejected as overbroad because only a single "agglomerable" material was disclosed. The C.C.P.A. reversed, stating that:

> [T]he board would limit appellant to claims involving the specific materials disclosed in the examples so that a competitor seeking to avoid infringing the claims would merely have to follow the disclosure in the subsequently-issued patent to find a substitute. However, to provide effective incentives, claims must adequately

[1] A long line of cases conclusively holds that working examples are not required to enable a claimed invention if the invention is otherwise disclosed. *See, e.g., In re Strahilevitz*, 212 U.S.P.Q. 561,563 (C.C.P.A. 1982) ("We recognize that working examples are *desirable* in complex technologies and that detailed examples can satisfy the statutory enablement requirement. ... Nevertheless, as acknowledged by the board, examples are not *required* to satisfy § 112, first paragraph.") (italics emphasis in original); *In re Borkowski*, 164 U.S.P.Q. 642, 645 (C.C.P.A. 1970) ("a specification need not contain a working example if the invention is otherwise disclosed"); *In re Long*, 151 U.S.P.Q. 640, 641 (C.C.P.A. 1966).

> protect inventors. To demand that the first to disclose shall limit his claims to what he has found will work to materials which meet the guidelines specified for "preferred" materials in a process such as the one herein involved would not serve the constitutional purpose of promoting progress in the useful arts.

As in *Goffe*, limiting the present claims to the specific preferred materials disclosed in the application would not adequately protect the invention, as it might allow an unscrupulous person to use the teachings of the application by substituting unexemplified embodiments.

Undue Experimentation[2]

The field of art is pharmacotherapeutics. In this field, a great deal of experimentation is routine and expected. For instance, the specification and U.S. Patent Application No. 09/944,049 incorporated by reference and as quoted above set forth the use of high-through-put screening to identify US28 modulators. Indeed, the various applications presently incorporated by reference illustrate the successful application of such methods to discovering US28 modulators on a wide scale.

In this regard, the Federal Circuit has pointed out that even a large amount of experimentation is not undue in the pharmaceutical arts. Courts have held, for instance, that if a specification teaches one embodiment and sets forth a method for determining dose/response, the experimentation required to determine a dose/response curve is not undue, even if the studies proved to cost approximately $50,000 and took 6-12 months to accomplish. *United States v. Telectronics,* 8 USPQ2d 1217 (Fed. Cir. 1988).

Overall Summary of the Wands Factors

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[2] That some experimentation may be necessary to identify operative species does not constitute a lack of enablement. As the Federal Circuit has stated, "the key word is 'undue', not 'experimentation' " in determining whether pending claims are enabled. *Wands*, 8 U.S.P.Q.2d at 1405 (Fed. Cir. 1988). Indeed, a considerable amount of experimentation is permissible if it is merely routine, or if the specification in question provides a reasonable amount of guidance for practicing the invention.

In light of the above discussion, Applicants believe the invention as claimed is fully enabled:

(i) the relative skill and experience of those in the arts of pharmacotherapeutics is traditionally very high;

(ii) the nature of the invention involves routine skills and screening assays for biological activity; (e.g., US28 receptor binding *in vitro,* animal bioassays);

(iii) the breadth of the claims as amended is well commensurate with the specification's disclosures; a great many exemplary compounds and methods of using them are disclosed in the instant application

(iv) the specification provides adequate guidance for all manipulations required to practice the invention, including most importantly the US28 receptor activity assays and methods of screening the compounds for *in vivo* activity;

(v) the specification provides working examples of many identified US28 receptor modulators and provides a prophetic example of such activity in U.S. Patent Application No. 09/944,049 which was incorporated by reference into the present specification;

(vi) the state of the pharmaceuticals art is high. Most importantly, in light of the specification teachings, it is predictable to practice the method of claim 29 by use of any one of diverse members of the genus of such modulators as well exemplified in the various applications which are incorporated by reference;

(vii) the predictability of the art with respect to the operability of the subject matter of the claims is high while the predictability of the art with respect to clinical efficacy is not the standard for patentability;

(viii) the quantity of experimentation necessary to practice the invention with exemplified and non-exemplified embodiments is what is routinely performed by a person of ordinary skill in the art of drug development given the nature of the compositions and the nature of the *in vivo* and *in vitro* test systems.

In view of the above *Wands* analysis, the Applicants respectfully request that the above rejection be reconsidered and withdrawn.

Response to the Rejection of Claims 5 and 29 for Alleged Obviousness-type Double-Patenting

Claims 5 and 29 stand rejected over claim 30 of co-pending application 09/944,049. Original claim 30 of co-pending application 09/944,049 recites:

> A method for treating an animal infected with cytomegalovirus (CMV) or at risk for infection by cytomegalovirus (CMV), comprising administering to the animal an agent that interferes with the expression or activity of US 28 or a US28 homolog.

Said claim 30 of the '049 application has been canceled without prejudice.

Response to the Rejection of Claims 29-33 under 35 U.S.C. §103(a) over Protiva et al. (4,243,805) in View of the Merck Manual of Diagnosis (17th Ed.) and Michelson.

**Standard of Review**

MPEP §2143 sets forth the basic requirements of a *prima facie* case of obviousness:

> To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.

Applicants address each of these factors in turn.

1. There is no Suggestion or Motivation to Combine the References.

Claims 29-33 stand rejected as allegedly unpatentable over Protiva et al. in view of the Merck Manual of Diagnosis and the Michelson reference. The Action correctly posits that Protiva et al. teaches some compounds of Formula I which have psychotropic and neurotropic activity and are useful as neuroleptics. The Action also indicates that the Merck Manual of Diagnosis discloses that CMV infection is manifested by "severe brain damage, CNS damage or CNS involvement in a human." The Action additionally posits that Michelson teaches that CMV causes mental retardation in humans and that CMV infects and/or replicates in a wide variety of cell types. The Action then asserts that one of ordinary skill in the art would have been

motivated to use the compounds taught by Protiva et al. to treat brain damage, CNS damage, or the other mentioned CNS disorders caused by CMV since these compounds have neurotropic and psychotropic activity and are useful as neuroleptics.

The Action's conclusion does not logically follow. The term "psychotropic agent" simply denotes an agent which can affect the psyche or mind. The term is broad and encompasses agents which have *opposite* effects. For instance, these terms encompass CNS depressants and CNS stimulants, mood elevators and mood depressors. Designating a compound as a psychotropic agent or a neurotropic agent does not indicate any particular CNS disturbance for which such an agent would be useful or harmful. One of ordinary skill in the art would appreciate that whether a psychotropic agent could be without effect, harmful, or beneficial with respect to the treatment of any particular CNS condition, including any CNS conditions associated with CMV infection, depends upon the therapeutic activity of the agent and the CNS condition. Thus, the teaching that an agent has psychotropic activity does nothing to indicate the particular condition(s) for which the compounds would be beneficial. Neither the Merck Manual or Michelson supply this deficiency as to which psychotropic agents, if any, would be beneficial in treating the subject conditions.

Applicants appreciate that the Protiva et al. reference further describes its agents as having "neuroleptic" activity with a high degree of cataleptic, anti-apomorphine, and central depressant action (see Abstract). More specifically, the Protiva et al. reference specification states at col. 27, lines 15 that the compound may be employed as "highly potent antipsychotics in the therapy of schizophrenic diseases." Not even in hindsight do the Merck Manual or Michelson suggest anti-apomorphine, cataleptic, or CNS depressant action, or antipsychotic therapy is indicated as a treatment of the CMV-induced CNS harm they discuss. In fact, where the Merck Manual discusses treatment of CMV infection it instructs the use of ganciclovir, foscarnet, and cidovir as well as passive CMV immune globulin. Neither the Merck Manual nor Michelson disclose or suggest *neuroleptic, antipsychotic, anti-cataleptic*, or *anti-apomorphine* activity as being useful in treating CMV-induced CNS conditions.

As the alleged motivation to combine the above cited references is simply not in evidence, Applicants respectfully request that the above grounds for rejection be reconsidered and withdrawn.

2. There was no Reasonable Expectation of Success.

There is no expectation of success that the particular neuroleptics taught by Protiva are broadly useful in treating the CMV-induced "CNS damage", "CNS involvement," or "severe brain damage" recited in the Merck Manual. or the Michelson reference. To illustrate, Michelson discloses the CMV-infection severe brain damage of deafness or mental retardation as sequelae of congenital CMV infection. On what scientific theory would one of ordinary skill in the art expect that deafness or mental retardation to be successfully treated by administration of the neuroleptic compounds taught by Protiva et al.

The claims have also been amended to further recite "wherein said administering slows the progression of CMV dissemination." If, assuming for the sake of argument, the Protiva et al. compounds were to be administered to treat such severe brain damage as deafness or mental retardation, the Protiva et al. compounds would be administered to treat the *sequelae* of the infection, not the *infection* itself. Such administration would not support an expectation by one of ordinary skill in the art that the progression of CMV dissemination would be slowed.

In the absence of any expectation of success for the proposed combination, Applicants respectfully request that the above grounds for rejection be reconsidered and withdrawn.

3. The References in Combination do Not Teach or Suggest All the Claim Limitations.

As amended claim 29 recites

> A method for treating CMV infection in a human, comprising administering to the human an effective amount of a US 28 receptor modulator capable of blocking or inhibiting the binding of a chemokine to the US28 receptor, wherein said modulator is a small organic compound of less than 800 daltons and said administering slows the progression of CMV dissemination in the human.

Claim 29 recites treating CMV *infection* in a human. The severe CNS harm cited in the Merck Manual is fairly viewed and diagnosed as sequelae of a congenital or other infection with CMV. If, assuming for the sake of argument, the Protiva et al. compounds were to be administered to treat such severe brain damage as deafness or mental retardation, the Protiva et al. compounds would be administered to treat the *sequelae* of the infection, not the *infection* itself and would not read on a method wherein the progression of CMV dissemination is slowed.

In view of all the above, Applicants respectfully request that the above ground for rejection be reconsidered and withdrawn.

Response to the Rejection of Claims 29-34 35 U.S.C. §103(a) as allegedly being unpatentable over Sindelar et al. in view of the Merck Manual of Diagnosis (17th Ed.) .and Michelson.

Sindelar discloses octoclothepin and methiothepin as "neurotropic, "psychotropic" and "neuroleptic" agents. As noted above, the term "psychotropic agent" simply denotes an agent which can affect the psyche or mind. The term "neurotropic agent" is perhaps even broader. It simply denotes an agent which can affect the nervous system. Again, both terms are broad and encompass agents which have *opposite* effects (e.g., CNS depressants and CNS stimulants, mood elevators and mood depressors). As before, designating a compound as a psychotropic agent or a neurotropic agent does not indicate any particular CNS disturbance for which such an agent would be useful or harmful.

With respect to the neuroleptic activity of octoclothepin and methiothepin, the above discussion of the disclosures of Protiva et al., the Merck Manual and Michelson reference apply just as strongly.

As above, assuming for the sake of argument, the Sindelar al. compounds were to be administered to treat such severe brain damage as deafness or mental retardation, the Sindelar et al. compounds would be administered to treat the *sequelae* of the infection, not the *infection* itself and would not read on a method wherein "the progression of CMV dissemination is slowed."

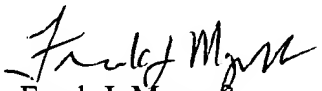
As none of the basic criteria of a *prima facie* case are met, Applicants respectfully request that the above rejection be reconsidered and withdrawn.

## CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 925-472-5000.

Respectfully submitted,



Frank J. Mycroft
Reg. No. 46,946

TOWNSEND and TOWNSEND and CREW LLP
Two Embarcadero Center, 8th Floor
San Francisco, California 94111-3834
Tel: 925-472-5000
Fax: 415-576-0300
Attachments
FJM:fjm
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